## A Convenient Synthesis of 1,4-Diaryl-3-(4-toluenesulfonyl)-azetidin-2-ones from Esters and Aldimines

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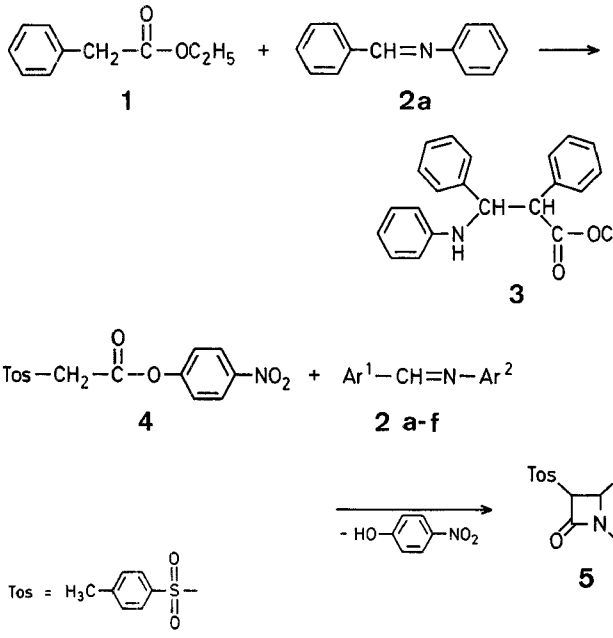
Azetidin-2-ones have been subject of intensive synthetic studies[1] since they are key components of many biologically active substances such as penicillins, cephalosporins, and other β-lactam antibiotics. We now report a convenient synthesis of 3-(4-toluenesulfonyl)-azetidin-2-ones **(5)** by the reaction of a tosylacetic acid ester (e.g. **4**) with aryl aldimines **(2)**. Reactions of 3-tosylazetidin-2-ones would enable one to introduce electrophilic groups into position 3 of the azetidinone ring and the tosyl group could be removed later.

The synthesis of azetidin-2-ones by the reaction of substituted acetyl chlorides with imines in the presence of amine bases is well known. Thus, tosylacetic acid[2] was treated with chlorinating agents such as thionyl chloride, oxalyl chloride, and phosphorus pentachloride; tosylacetyl chloride, however, was not obtained even when the chlorination was carried out under cooling with ice. Because of its high reactivity, the methylene group of tosylacetic acid appears to be vulnerable to attack by the chlorinating reagents[3]. Therefore an ester of tosylacetic acid was prepared as a synthon for the acid chloride. As it was reported[4] that the reaction of ethyl phenylacetate **(1)** with benzylideneaniline **(2a)** gave the ethyl 3-aminopropanoate derivative **(3)**, 4-nitrophenyl tosylacetate **(4)** (the nitrophenoxy group is known to be a good leaving group) was used as the C-2—C-3 component of the azetidinone ring.




When an equimolar mixture of **4**, benzylideneaniline (**2a**; $Ar^1 = Ar^2 = C_6H_5$), and triethylamine in anhydrous dichloromethane was heated under reflux for 24 h, the cyclization reaction gave the new azetidinone (**5a**, $Ar^1 = Ar^2 = C_6H_5$) in a poor yield (16%). The structure of the azetidinone obtained was established by its $^1$H-N.M.R. spectrum (two doublets at $\delta = 5.59$ and 4.44 ppm, 3-H and 4-H of the azetidinone ring) and I.R. spectrum ($\nu = 1750$ cm$^{-1}$, lactam carbonyl).

The yield of the cyclization reaction was improved (but not optimized) by employing imidazole instead of triethylamine as the cyclizing reagent. Thus, when the reaction described was carried out in the presence of imidazole, the yield of the azetidinone **5a** increased (see Table).

This method is convenient to synthesize azetidin-2-ones from imines and a carboxylic acid of which an acid chloride is difficult to prepare. The activated ester **4** is a crystalline compound and can be stored at a room temperature. Aliphatic aldimines appear not to give corresponding azetidin-2-ones under the conditions described.

**4-Nitrophenyl Tosylacetate (4):**
A mixture of tosylacetic acid (2.14 g, 10 mmol), 4-nitrophenol (1.39 g, 10 mmol), and dicyclohexylcarbodiimide (2.12 g, 10.3 mmol) in anhydrous ethyl acetate (30 ml) is stirred at 60 °C for 17 h. The dicyclohexylurea formed is removed by filtration and the filtrate is evaporated to

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**Table.** 1,4-Diaryl-3-tosylazetidin-2-ones **5** prepared

| Product No. | $Ar^1$ | $Ar^2$ | Yield[a] [%] | m.p.[b] [°C] | Molecular formula[c] | I.R. (Nujol) $\nu_{C=O}$ [$cm^{-1}$] | $^1$H-N.M.R. ($CDCl_3$) $\delta$ [ppm] 3-H (d) | 4-H (d) |
|---|---|---|---|---|---|---|---|---|
| **5a** | $C_6H_5$ | $C_6H_5$ | 47 | 173.5–174.5° | $C_{22}H_{19}NO_3S$ (377.4) | 1750 | 4.44 ($J$ = 2.5 Hz) | 5.59 ($J$ = 2.5 Hz) |
| **5b** | 4-$O_2N$—$C_6H_4$ | 4-Cl—$C_6H_4$ | 46 | 230–231° | $C_{22}H_{17}ClN_2O_5S$ (456.9) | 1758 | 4.45 ($J$ = 2.5 Hz) | 5.69 ($J$ = 2.5 Hz) |
| **5c** | 4-Cl—$C_6H_4$ | 4-Cl—$C_6H_4$ | 46 | 182–184° | $C_{22}H_{17}Cl_2NO_3S$ (446.3) | 1757 | 4.43 ($J$ = 3.0 Hz) | 5.54 ($J$ = 3.0 Hz) |
| **5d** | 4-$O_2N$—$C_6H_4$ | $C_6H_5$ | 42 | 246–246.5° | $C_{22}H_{18}N_2O_5S$ (422.4) | 1758 | 4.42 ($J$ = 2.5 Hz) | 5.72 ($J$ = 2.5 Hz) |
| **5e** | 4-Cl—$C_6H_4$ | 3-$O_2N$—$C_6H_4$ | 48 | 227.5–228° | $C_{22}H_{17}ClN_2O_5S$ (456.9) | 1760 | 4.46 ($J$ = 3.0 Hz) | 5.65 ($J$ = 3.0 Hz) |
| **5f** | $C_6H_5$ | 4-Cl—$C_6H_4$ | 43 | 202–203° | $C_{22}H_{18}ClNO_3S$ (411.9) | 1750 | 4.42 ($J$ = 2.5 Hz) | 5.50 ($J$ = 2.5 Hz) |

[a] Yield of crystallized product.
[b] Not corrected.
[c] Satisfactory microanalyses obtained: C ±0.28, H ±0.18, N ±0.29.

dryness under reduced pressure to afford a viscous oil. Trituration with ether gives the crude solid product which is recrystallized from acetone/hexane to give colorless prisms; yield: 2.79 g (83%); m.p. 123–123.5 °C.

| | | | | |
|---|---|---|---|---|
| $C_{15}H_{13}NO_6S$ | calc. | C 53.72 | H 3.91 | N 4.18 |
| (335.33) | found | 53.59 | 3.76 | 4.36 |

I.R. (Nujol): $\nu$ = 1762 (C=O), 1530, 1342 (—$NO_2$), 1335, 1148 (—$SO_2$—) $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 2.40 (s, 3 H); 4.25 (s, 2 H); 7.1–8.4 ppm (m, 8 H).

**1,4-Diaryl-3-tosylazetidin-2-ones (5a–f); General Procedure:**
A solution of 4-nitrophenyl tosylacetate (**4**; 0.34 g, 1 mmol), the Schiff base **2** (1 mmol), and imidazole (0.07 g, 1 mmol) in anhydrous dichloromethane (5 ml) is heated under reflux for 15 h, washed with water (5 ml), and dried with sodium sulfate. Evaporation of the dichloromethane and trituration with methanol gives the crude solid which is recrystallized from dichloromethane/methanol.

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